EXHIBIT B

William J. Heller, Esq.
McCARTER & ENGLISH, LLP
Four Gateway Center
100 Mulberry St.
Newark, New Jersey 07102
Phone: (973) 622-4444
Facsimile: (973) 624-7070

Of Counsel:
Lisa B. Pensabene, Esq.
Dominick A. Conde, Esq.
Joshua I. Rothman, Esq.
FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, New York 10112
Phone: (212) 218-2100
Facsimile: (212) 218-2200

Henry B. Gutman, Esq.
Robert A. Bourque, Esq.
Noah M. Leibowitz, Esq.
SIMPSON THACHER & BARTLETT LLP
425 Lexington Avenue
New York, New York 10017
Phone: (212) 455-2000
Facsimile: (212) 455-2502

Attorneys for Plaintiffs
DAIICHI SANKYO COMPANY, LIMITED
and DAIICHI SANKYO, INC.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

DAIICHI SANKYO COMPANY, LIMITED and DAIICHI SANKYO, INC., Plaintiffs and Counterclaim Defendants, v. MYLAN PHARMACEUTICALS INC., MYLAN LABORATORIES INC., MATRIX LABORATORIES LTD., and MYLAN INC. Defendants and Counterclaim Plaintiffs.	Civil Action Nos. 2:06-3462, 07-3039, and 08-2752 (WJM)(MF) (Consolidated) **PLAINTIFFS' POST-TRIAL BRIEF**

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases

Statutes & Administrative Codes

PRELIMINARY STATEMENT

Mylan admits, as it must, that its generic olmesartan medoxomil products would infringe Daiichi Sankyo's olmesartan medoxomil patent, U.S. Patent No. 5,616,599. Mylan's sole defense -- on which it bears the burden of proof by clear and convincing evidence -- is that the Daiichi Sankyo patent should never have been granted because olmesartan medoxomil is obvious over the prior art -- specifically, DuPont's U.S. Patent No. 5,137,902 ("the '902 patent").

Starting with the actual chemical structure of olmesartan medoxomil and employing the "20/20 hindsight" this starting point provides, Mylan argues that the olmesartan portion of the compound is obvious because it differs from one of the examples found in DuPont's '902 patent by only a single oxygen atom. That this difference totally changes the "personality" of the substituent in question is a detail Mylan ignores. To enhance oral activity by adding medoxomil to the compound to create a prodrug, claims Mylan, is equally obvious because medoxomil was previously known. Again, the facts that medoxomil had never been used before in a compound of this sort, and that the consequences of doing so were entirely unknown, are overlooked by Mylan. A mystery novel is no mystery when one begins by reading the last page. That is exactly the approach Mylan has taken in this case.

When the analysis instead begins where legally it must -- from the vantage point of the person of ordinary skill in April 1991 -- the conclusion is very different. Mylan's obviousness argument rests on four premises, each of which must be proven for Mylan to succeed and none of which was proven by the requisite clear and convincing evidence standard (or any standard) at trial.

First, Mylan failed to prove that one of ordinary skill would have selected the '902 patent compounds as leads. Instead, the evidence at trial proved that as of April 26, 1991 (the relevant date here for considering the scope and content of the prior art), several leads other than the '902 patent compounds were better starting points. Mylan's Dr. Weinstock admitted that the '902 patent compounds were not the only, and indeed not even the best, possible leads as of April 1991. Only hindsight can explain Mylan's choice of the '902 patent compounds.

Second, Mylan failed to prove that one of ordinary skill in the art would have modified the '902 patent compounds to arrive at olmesartan medoxomil. Rather, the evidence at trial showed that the '902 patent compounds could have been modified in hundreds of different ways at several different positions. Nothing at the time taught one of ordinary skill in the art to focus on the 4-position of the '902 patent compounds and to modify that position in precisely the way necessary to arrive at olmesartan medoxomil. To the contrary, the prevailing wisdom in the field -- the structure activity relationship ("SAR") from the DuPont work followed by every research group ***other*** than Daiichi Sankyo -- taught that a lipophilic group at the 4-position yielded best activity. Indeed, the '902 patent emphasized the importance of lipophilicity, as Mylan's medicinal chemistry expert admitted. Olmesartan medoxomil, on the other hand, has a hydrophilic, hydroxyisopropyl substituent at that position, with exactly the opposite personality and properties. Further, as Mylan's experts admitted, the prodrug approach used by olmesartan medoxomil was considered by the art to be an unpredictable last resort. That is, even if one had started, improbably, with the '902 patent compounds as leads, nothing in the art would have led to olmesartan medoxomil.

Third, Mylan failed to prove that one of ordinary skill in the art would have had any reasonable expectation of obtaining a compound that possesses all the properties of

olmesartan medoxomil. As Mylan's chemistry expert admitted, just a single atom change to the imidazole ring of an ARB compound would result in "very, very different" properties, which would be unknown until the compound was made and tested. If anything, based on the DuPont SAR, a structure like olmesartan medoxomil's would have been expected to fail. An ordinary researcher would not have had any reasonable expectation of obtaining a compound with olmesartan medoxomil's unique combination of properties, including better affinity for the angiotensin receptor, improved oral potency, superior selectivity and longer duration of action relative to the benchmark losartan.

Fourth and finally, Mylan failed to prove that the objective indicia favor a finding of obviousness. Overwhelming evidence established that olmesartan medoxomil has surprising and unexpected properties, impossible to predict in April 1991, including better blood pressure lowering ability, better potency, inverse agonism, insurmountable antagonism, lack of drug interactions and unexpected health benefits beyond just lowering blood pressure. Further, the commercial success of Daiichi Sankyo's olmesartan medoxomil family of products, growing from the seventh ARB to enter a crowded market to become a blockbuster, with sales of nearly $1.3 billion in calendar year 2008, provides powerful proof that prescribing physicians do not consider olmesartan medoxomil just a "me-too" product. In April 1991 there was a need for a better ARB and the mainstream medical community has accepted olmesartan medoxomil as meeting that need -- precisely the reason Mylan wants to copy ***that*** compound, rather than any of the others.

On a more fundamental level, Mylan does not and cannot explain why, if creating olmesartan medoxomil was so obvious, no one else did it. There were hundreds of researchers around the world hard at work trying to find a better ARB than losartan, yet not one reported

ever trying a hydroxyisopropyl at the 4-position until Daiichi Sankyo did -- not the pioneers at DuPont, who created losartan (and various second generation compounds, including those in the '902 patent) and not any of the other major pharmaceutical companies that created other commercial ARBs. The simple explanation was provided by a witness with first-hand knowledge, Dr. Timmermans of DuPont, who explained that what the Daiichi Sankyo inventors did -- using a hydrophilic substituent at the 4-position -- was "completely counterintuitive." As the Federal Circuit has explained, "[i]f the invention here would not have been obvious to one of extraordinary skill, it follows that in this case it would not be obvious to one with lesser skills." *Specialty Composites v. Cabot Corp.*, 845 F.2d 981, 991 (Fed. Cir. 1988).

In sum, Mylan failed at trial to meet its burden of proving the Daiichi Sankyo patent obvious by clear and convincing evidence. Therefore judgment should be entered for Daiichi Sankyo.

ARGUMENT

I. Mylan Bears The Burden Of Proving By Clear And Convincing Evidence That The '599 Patent Is Obvious

Obviousness is determined as a matter of law based on the following underlying factual inquiries: (1) the level of ordinary skill in the art; (2) the scope and content of the prior art; (3) the differences between the claimed invention and the prior art; and (4) the objective indicia of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

A patent is presumed valid. 35 U.S.C. § 282. Accordingly, Mylan must prove each of the *Graham* elements by clear and convincing evidence. *Beckson Marine, Inc. v. NFM, Inc.*, 292 F.3d 718, 725 (Fed. Cir. 2002). If Mylan fails to prove even one element of its obviousness defense by clear and convincing evidence, Daiichi Sankyo prevails. *E.I. DuPont de Nemours & Co. v. Mallinckrodt, Inc.*, 654 F. Supp. 890, 905 (S.D. Ohio 1987), *aff'd*, 833 F.2d

1022 (Fed. Cir. 1987).[1] Moreover, where the challenging party relies principally upon the same prior art considered by the PTO during years of examination -- as Mylan does here -- this evidentiary burden is "especially difficult." *Al-Site Corp. v. VSI Int'l, Inc.*, 174 F.3d 1308, 1323 (Fed. Cir. 1999).

For chemical compounds, the structure of the compound and its properties are inseparable considerations in the obviousness determination. *See In re Sullivan*, 498 F.3d 1345, 1353 (Fed. Cir. 2007); *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963). To prove obviousness of a chemical compound a patent challenger must prove by clear and convincing evidence that a person of ordinary skill in the art: (1) would have selected a particular "lead compound" as a starting point for making chemical modifications, (2) would have been motivated to make the specific chemical modifications to that lead compound needed to obtain the invention, and (3) would have had a reasonable expectation that those modifications would result in the properties of the invention. *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008) (citing *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1742 (2007)); *Takeda Chem. Indus. v. Alphapharm Pty.*, 492 F.3d 1350, 1355 (Fed. Cir. 2007).

The patent challenger also must prove by clear and convincing evidence that the objective indicia, such as unexpected results, commercial success and copying, support a finding of obviousness. The burden of proof -- even with respect to the objective indicia of non-obviousness -- remains with the patent challenger and never shifts. *RCA Corp. v. Applied Digital Data Systems, Inc.*, 730 F.2d 1440, 1444 (Fed. Cir. 1984).

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[1] Clear and convincing evidence must "place in the ultimate factfinder an abiding conviction that the truth of [the] factual contentions is 'highly probable.'" *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984) Mylan's evidence would meet this standard only if it "instantly tilted the evidentiary scales in the affirmative" when weighed against the evidence offered in opposition. *Id; see also Intel Corp. v. United States Int'l Trade Comm'n*, 946 F.2d 821, 829-30 (Fed. Cir. 1991).

Mylan has failed to meet its burden at every step of the analysis.

II. Mylan Has Failed To Prove That Olmesartan Medoxomil Is Obvious

A. The Level Of Ordinary Skill In The Art

Obviousness is judged from the perspective of a hypothetical person of ordinary skill in the art. *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138 (Fed. Cir. 1985). As Dr. Lipinski explained at trial, one of ordinary skill either would be a medicinal chemist with a Ph.D. or a lesser degree with a few years of experience. PFF [2] ¶ 87. This level of skill is consistent with that of the researchers at other companies, like Pfizer, during the contemporaneous period. PFF ¶ 88. Mylan advances a definition that is indicative of a person of slightly greater skill.

Regardless of which standard is applied, the parties agree that a person of ordinary skill in the art would have known how to analyze structure-activity relationships from data in the literature. PFF ¶ 91. Such a person would have followed, rather than departed from, the teachings, trends and theories disclosed in the art, and would have avoided basing research on a theory not established and accepted in the field. *Life Tech. Inc. v. Clontech Labs.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000); PFF ¶ 93. As Dr. Lipinski testified, under either Daiichi Sankyo's or Mylan's definition of the person of ordinary skill in the art -- indeed, even to an expert -- olmesartan medoxomil would not have been obvious. PFF ¶ 94.

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[2] "PFF " refers to Plaintiffs' Proposed Findings of Fact, filed concurrently herewith.

B. Scope And Content Of The Prior Art

As of April 26, 1991,[3] the relevant prior art included patents and papers on losartan and numerous second generation compounds invented by DuPont and other companies. To build its case, Mylan culls through this art, using the olmesartan medoxomil invention as a guide, and picks as its leads not the ***best*** compounds, but those which in hindsight are "closest" structurally to the invention. Then, rather than follow the overwhelming weight of the art -- including the '902 patent -- which taught that a lipophilic group was preferred at the 4-position, Mylan argues that an ordinary researcher would have followed "outliers," obscure references and outdated theories to pick a hydrophilic group instead. Mylan's approach is entirely based upon hindsight, which is not permitted under the law. *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138 (Fed. Cir. 1985) ("The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time.").

1. The Prior Art As Of April 26, 1991 Demonstrates The Importance Of A Lipophilic Group At The 4-position

a. DuPont's Invention Of Losartan

In September 1989, DuPont publicly announced the first ARB potent enough for use in humans, DuP-753, later known as losartan. PFF ¶ 116. Losartan retained the imidazole ring of earlier Takeda compounds, with a lipophilic chlorine atom at the 4-position. PFF ¶ 121. As Dr. Weinstock admitted, the "highlights of the DuPont work" and "advances they made as they proceeded in their research" all have lipophilic groups at the 4-position. PFF ¶ 117.

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[3] Obviousness is determined as of the date of the invention. 35 U.S.C. § 103(a). Here, because the invention of olmesartan medoxomil took place outside the United States, 35 U.S.C. § 120 fixes the invention date at the filing date of the patent application claiming olmesartan medoxomil -- April 26, 1991. There is no dispute between the parties on this issue.

DuPont's research leading to losartan was reported in U.S. Patent No. 5,138,069 ("the '069 patent"). PFF ¶ 123. The '069 patent describes over 400 compounds that were synthesized and tested as a part of DuPont's ARB research and provided specific binding affinity data for over 200 of those compounds. PFF ¶ 209.

b. DuPont's Second Generation ARB Compounds

DuPont itself continued to look for improvements to losartan following its established SAR (including the preference for lipophilicity at the 4-position for best activity). PFF ¶¶ 126, 127, 196.[4] In mid-April 1991, at two important national scientific conferences, DuPont reported "a new series of 4-perfluoro-alkylimidazole" compounds that "exceed the potency of DuP 753 [losartan]," the showcased compound being DuP 532. PFF ¶¶ 128, 129. DuP 532 changed the 4-position of losartan from chlorine to an even more lipophilic substituent, containing multiple fluorine atoms. PFF ¶¶ 131-133.

On February 4, 1991, DuPont filed the patent application that led to issuance of the '902 patent, disclosing six compounds with alkyl groups at the 4-position. PFF ¶139. Compared with losartan, the change to alkyl substituents again increased lipophilicity at the 4-position. PFF ¶ 138. The '902 patent issued to DuPont on August 11, 1992, long after the invention of olmesartan medoxomil. PFF ¶¶ 140, 12. While the '902 patent was not actually known or available to the Daiichi Sankyo inventors prior to the invention of olmesartan medoxomil, it is prior art by operation of law under 35 U.S.C. § 102(e).

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[4] In early 1991, there were no clinical trial results for losartan, and it was unclear whether losartan would be approved by the FDA. PFF ¶ 125 ("The first generation molecule, it could fail.").

c. Other Companies' Second-Generation ARB Compounds

DuPont's announcement of losartan as a clinical candidate sparked a "frenzy among other companies to improve upon losartan." PFF ¶¶ 150, 154. Losartan was a good start, but a more potent ARB that could lower blood pressure further for a longer period of time was needed. PFF ¶¶ 151, 153.

By April 1991, Merck, Ciba-Geigy, Takeda and Eisai, among others, had publicly disclosed their own "second generation" ARB compounds. PFF ¶¶ 155, 156. Some of the prior art second generation compounds use different ring structures than losartan, and different structures corresponding to the 1-, 2- and 5-positions. PFF ¶¶ 163-166. One common theme among the second generation ARB compounds, however, is a lipophilic group at the position corresponding to losartan's imidazole 4-position.[5] PFF ¶¶ 158-161.

2. The Prior Art Taught Away From Using A Hydrophilic Substituent At The 4-Position Of The Imidazole Ring

The very prior art relied on by Mylan -- the '069 patent and the second generation '902 patent -- teach that it is better to use a lipophilic group, rather than a hydrophilic group, at the 4-position. On the question of teaching away, just as on all elements of the obviousness inquiry, the burden of proof is Mylan's. It is not Daiichi Sankyo's burden to prove that the prior art taught away from the invention. It is Mylan's burden to prove by clear and convincing evidence that it did not. *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1378 (Fed. Cir. 2006) (patent challenger must show that prior art teachings motivated the modification rather than taught away).

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[5] Dr. Weinstock pointed to a few isolated compounds in a ***non-prior art*** publication with non-lipophilic groups at the 4-position. None were demonstrated to be prior art, there was no data on any and they were referenced among more than a hundred compounds with lipophilic groups at the 4-position. PFF ¶¶ 424, 426.

a. DuPont's Second-Generation ARB Compounds Independently Teach The Preference For Lipophilicity At The 4-Position

The analysis need go no further than DuPont's own second-generation compounds -- the '902 patent compounds and DuP 532 -- which all increased lipophilicity at the 4-position in order to improve upon losartan. PFF ¶¶ 131-33, 138, 197-203. Indeed, Dr. Weinstock explicitly admitted this as to the '902 patent:

> the '902 patent ***teaches that a lipophilic*** but not an electron-withdrawing group, at the 4-position of the imidazole gives compounds with potent binding activity and are orally active
>
> [which] ***emphasizes the importance of lipophilic-type binding forces*** between the surface of the antagonist and the receptor."

PFF ¶¶ 200-201; *see also* PFF ¶ 202 ("you can infer because these are the compounds that lipophilicity is … an important part of the ['902] patent").[6]

b. The Data In DuPont's '069 Patent Teach That Lipophilic Substituents Are Needed At The Imidazole 4-Position For Best Activity

The data in the '069 patent also disclosed the DuPont SAR -- preferring lipophilic groups at the 4-position for best activity. PFF ¶¶ 204-215. A medicinal chemist of ordinary skill also would have considered the overwhelming number of compounds in the '069 patent with lipophilic groups at the 4-position as indicating a clear direction and preference. PFF ¶¶ 216-20 "[B]y looking and seeing what [the DuPont scientists] actually made, that tells you what they were thinking because they were trying to make active compounds." PFF ¶ 220 ("the chemists voted . . . with their hands."). And, DuPont selected losartan, with a lipophilic chlorine at the 4-position, as a clinical candidate. PFF ¶¶ 117, 120. *See Eli Lilly*, 364 F.Supp. 2d at 846 (choice

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[6] DuPont's later description of DuP 532 said that the success of this work "seemed to confirm our original hypothesis that the 4-position of the imidazole is most appropriately substituted with a large, lipophilic and electron-withdrawing group." PFF ¶ 199.

of compound as a clinical candidate "reflected the ultimate preference" for a particular type of group and was evidence of teaching away)

An evaluation of the most active compounds in the '069 patent similarly shows the importance of a lipophilic group at the 4-position for best activity. PFF ¶¶ 221-227. Of the 30 compounds in the '069 patent with the highest binding affinity, 27 contain lipophilic groups at the 4-position. PFF ¶ 223.[7] Dr. Weinstock never undertook this analysis. PFF ¶ 222.

A simple comparison of the lipophilic and non-lipophilic compounds from the '069 patent reveals the same preference. PFF ¶¶ 236-39. Dr. Weinstock admitted that an ordinary medicinal chemist would establish an SAR by looking at compounds with the identical 1, 2 and 5-positions and varying only the 4-position – referred to as a subseries analysis. PFF ¶ 236. Drs. Timmermans and Lipinski undertook this "apples to apples" subseries analysis and explained that the advantage of lipophilicity at the 4-position is evident across all of the different subseries in the '069 patent. PFF ¶¶ 238-39.

In contrast, ignoring the proper subseries analysis, and impermissibly using the invention as a guide, Dr. Weinstock picked out five examples of compounds with high binding affinity and a neutral or hydrophilic group at the 4-position and testified that these "exceptions" or "outliers" suggested using hydrophilic groups at the 4-position instead. PFF ¶¶ 240, 243. However, even Dr. Weinstock's five "exceptions", when placed in the context in their proper subseries, confirmed the importance of lipophilicity at the 4-position for best activity. PFF ¶ 241. Dr. Weinstock admitted that for each of his supposed exceptions, the '069 patent provides an example of a compound with identical 1-, 2-, and 5-positions but with a ***lipophilic*** group at

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[7] For each of the remaining three compounds (two with the same neutral group and one with a hydrophilic group at the 4-position), corresponding compounds exist among the top 30 that are identical at other positions, but have lipophilic 4-positions and show better binding affinity, as Dr. Weinstock admitted. PFF ¶¶ 224-27.

the 4-position and, in each instance, the compounds with lipophilic 4-positions were more active. PFF ¶¶ 242, 246-49; *see also* 244-45.[8] *See Eli Lilly*, 471 F.3d at 1379 (No obviousness; teaching away when prior art reference data demonstrated that compound without halogen group had less activity than compound with preferred halogen group).

Finally, a comparison of the regioisomer pairs (compounds with the 4 and 5 groups switched) in the '069 patent further confirms the importance of a lipophilic 4-position. PFF ¶¶ 255-64; *see also* PFF ¶ 265. In each instance, the regioisomer with the more lipophilic group at the 4-position had higher binding affinity than the regioisomer with the less lipophilic group at that position. PFF ¶¶ 259-63. In fact, as the '069 patent explicitly states: "In all series, the more rapidly eluted [more lipophilic] isomer of a given pair has greater biological potency than the less rapidly eluted [less lipophilic] isomer." PFF ¶ 264.

c. Other Second-Generation ARB Compounds Confirm The '069 SAR

Likewise, others in the field followed DuPont's teaching of a lipophilic group at the 4-position. PFF ¶¶ 158-61. For example, it is undisputed that Merck's L-158,809, Eisai's E-4177, candesartan cilexetil, and valsartan are all prior art compounds and each contains a lipophilic substituent corresponding to the 4-position. PFF ¶¶ 156, 160-161.[9] In fact, Dr.

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[8] Dr. Weinstock cited examples with lipophilic groups at the 4-position as exceptions (the 265 series), but then admitted on cross examination that they were not exceptions at all. PFF ¶¶ 250-253. Mylan made its own table of compounds in the '069 patent with biphenyl tetrazoles at the 1-position. Regardless of the arrangement of the data, the appropriate subseries analysis reveals the same thing -- for every compound with a neutral or hydrophilic group at the 4-position there is a corresponding compound with a lipophilic group at the 4-position with higher binding affinity. PFF ¶¶ 228-35.

[9] Dr. Weinstock tried to rely on supposed counterexamples from a 1992 non-prior art patent review article on ARBs by Buhlmayer, but none was shown to be prior art. PFF ¶ 424. Meanwhile, the overwhelming majority of compounds in the Buhlmayer paper contain a lipophilic group at the 4-position (or the equivalent). PFF ¶¶ 423, 426. The

Weinstock admitted that Sanofi researchers, working prior to April 26, 1991, "followed the teaching of lipophilicity at the 4-position" to discover irbesartan (now a commercial ARB) with a lipophilic 4-position. PFF ¶ 158.

d. DuPont's Publications Confirm The Advantage Of Lipophilicity Of The 4-position And Corroborate The Appropriate Interpretation Of The '069 Patent SAR

While Dr. Weinstock testified that the '069 patent did not teach a preference for the lipophilicity for best activity, he admitted that he was not aware of a single scientific paper that supported his reading of the '069 patent data. PFF ¶¶ 268-270. On the other hand, contemporaneous articles written by DuPont scientists (and others) based on the '069 patent data corroborated the correct interpretation of that data. PFF ¶¶ 268-70. According to those articles, the '069 patent data demonstrated that the 4-position was "most appropriately substituted by a large, lipophilic and electron-withdrawing group." PFF ¶¶ 271. In contrast to Dr. Weinstock's testimony, these contemporaneous, non-litigation analyses confirm that the DuPont '069 patent data taught the importance of a lipophilic substituent at the 4-position.[10] PFF ¶ 271.

Mylan attempts to make much of the notion that no prior art article states, in so many words, that a lipophilic substituent is preferred at the imidazole 4-position.[11] But, a

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paper also identifies "best known" compounds, which contain lipophilic groups at the 4-position (except neutral eprosartan) and are identified as prior art. PFF ¶ 425.

[10] The Carini 1991 article, although published a few months after the April 1991 priority date, was written and submitted for publication ***before*** the priority date and provides contemporaneous corroboration that Dr. Weinstock's litigation driven analysis is contrary to the understanding in the field at the relevant time. PFF ¶¶ 272-276.

[11] The two DuPont publications Mylan relies on are about older pre-losartan, pre-biphenyl tetrazole series of compounds. PFF ¶ 282. Dr. Weinstock testified that the papers on the pre-losartan compound series were less relevant than the biphenyltetrazole series losartan and second generation compounds. PFF ¶ 283. Regardless, the papers on the pre-losartan compound series are consistent with the trend for lipophilicity at the 4-position -- the data demonstrate the preference for lipophilicity and the papers explicitly describe the

researcher of ordinary skill in the art could see the trend simply by reading the data and the compounds from the '069 and '902 patents. PFF ¶ 281. It is undisputed that an ordinary medicinal chemist would be able to analyze structure-activity relationships based on data in patents and would not expect or need DuPont to spell out the teachings word for word in text. PFF ¶¶ 281.

C. Differences Between The Prior Art And The Challenged Claim

1. Mylan Failed To Prove That A Person Of Ordinary Skill In The Art Would Have Selected the '902 Patent Compounds As Lead Compounds

To satisfy the first element of its obviousness defense, Mylan must prove by clear and convincing evidence that a person of ordinary skill in the art would have selected a particular "lead compound" as a starting point for making chemical modifications. *Eisai Co.*, 533 F.3d at 1359 (citing *KSR*, 127 S. Ct. at 1742).

Dr. Weinstock admitted that "you would certainly consider the most potent compounds as a possible starting point." PFF ¶¶ 292-294. A medicinal chemist would pick the "best compound" as a lead because "it increases your chances of success." PFF ¶¶ 295-97. In addition, an ordinary medicinal chemist would prefer a compound with a robust package of real data. PFF ¶¶ 298-301, 374. ("[Y]ou see which compounds have the best data package, the most complete data package.").

The evidence demonstrated that losartan and other second generation compounds would have been more attractive leads in April 1991 than the '902 patent compounds. PFF ¶¶ 301-380. Unquestionably, losartan was the most thoroughly characterized and widely studied

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regioisomer comparisons, with lipophilic substituents at 4-position resulting in better binding. PFF ¶¶ 277, 284-91.

ARB. PFF ¶ 304. In reality, most companies in the field used losartan as a lead and as the reference compound against which new compounds were measured. PFF ¶¶ 303, 305.

Additionally, by April 1991, substantial data were publicly available on at least four second-generation compounds: Merck's L-158,809; DuPont's DuP 532; Ciba-Geigy's valsartan; and Eisai's E-4177. PFF ¶¶ 209-354. These second-generation ARBs had real data that had been published, demonstrating much greater potency than losartan: binding affinities of 180 times (L-158,809), 100 times (E-4177), 7 times (DuP 532), and 2 times (valsartan) better than losartan. PFF ¶¶ 310-14, 324-28, 333, 338-41, 346-49, 376. As to oral activity, DuP 532 had three times the activity of losartan and L-158,809 had almost perfect oral bioavailability. PFF ¶¶ 335, 318.

In contrast, the '902 patent provides no actual data on any example -- nothing on binding affinity, intravenous activity, specificity or testing in other species. PFF ¶¶ 356-62. Mylan looks to the '902 patent's general statement that the "compounds which we have tested" exhibited "equal or greater oral activity" than the most active compounds "disclosed and tested" in the '069 patent. PFF ¶¶ 363; *see also* PFF ¶¶ 362, 364-67. But, the most that an ordinary medicinal chemist could have gleaned from this statement is that there was oral activity at a dose of 30 mg/kg, the dose tested in the '069 patent. PFF ¶¶ 370-72. This would not make the '902 patent compounds the most attractive leads: valsartan reported equal activity and L-158,809 and DuP 532 had much better activity. PFF ¶¶ 317, 330, 335, 351-52, 372, 377. Tellingly, Dr. Weinstock never challenged any of these possible leads, and admitted on cross examination that L-158,809 and DuP 532 were significantly ***more*** potent.[12] PFF ¶¶ 314, 335.

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[12] At trial, Dr. Weinstock added a belated opinion that the regioisomer of losartan (Example 118 of the '069 patent) could have been a lead. This was soundly discredited by Dr. Weinstock's admissions that losartan's regioisomer had half the activity of losartan

In sum, the evidence at trial demonstrated that a medicinal chemist of ordinary skill in April 1991 would have considered losartan and a number of second-generation compounds, including L-158,809, DuP 532, E-4177, and valsartan more attractive as lead compounds than the examples of the '902 patent. PFF ¶¶ 303-305, 323, 337, 345, 354, 373-380. As the Federal Circuit has explained, a compound is not obvious when "the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation." *Takeda Chem. Indus.*, 492 F.3d at 1359-60; *Yamanouchi Pharm. Co. v. Danbury Pharm., Inc.*, 231 F.3d 1339, 1344-45 (Fed. Cir. 2000) (invention not obvious where the defendant "did not show the required motivation for selecting example 44 as a lead compound"). That is precisely the case here.

2. Olmesartan Medoxomil Is Structurally Distinct From The Proposed '902 Lead Compounds

Even if Mylan had met its burden to prove that the '902 patent compounds would be selected as leads -- and it did not -- olmesartan medoxomil differs structurally from those compounds in several significant respects at the 4- and 5-positions. PFF ¶¶ 382-85.

At the 4-position of the imidazole ring, all six '902 patent compounds have a lipophilic alkyl group (belonging to the "alkane" class) while olmesartan has a completely different class of substituent, with very different properties -- a hydrophilic alcohol group.[13] PFF

(consistent with the trend for all regioisomers) and that DuPont had chosen losartan over Example 118. PFF ¶¶ 306-308. The only way to arrive at Example 118 as a lead is a hindsight use of the olmesartan invention as a guide.

[13] It is undisputed that hydroxyisopropyl is normally a hydrophilic group. PFF ¶ 415; *see also* PFF ¶¶ 394-95. Mylan looks to an unverified contention interrogatory response to try to argue otherwise. This response states Daiichi Sankyo's position: that alcohols and alkyls have opposite properties. The phrase suggesting that the hydroxyisopropyl group itself is "weakly lipophilic" was mistaken, as is clear from the rest of the interrogatory response, Drs. Lipinski's and Timmermans' expert reports, depositions and trial testimony, and Dr. Weinstock's testimony at deposition and at trial. PFF ¶¶ 413-14.

¶ 386, 391-92. Alkanes and alcohols are recognized by medicinal chemists as "radically different" groups. PFF ¶¶ 387-90, 393-94. For example, propane (an alkane used as cooking gas) is a lipophilic gas, while isopropanol (used as rubbing alcohol) is a hydrophilic liquid, even though their chemical structures differ by the same hydroxy group (basically one oxygen) that distinguishes olmesartan from the '902 patent compounds. PFF ¶¶ 389, 391, 396.

In fact, during patent prosecution, the patent examiner specifically recognized the hydroxy group as a structural difference from the '902 patent compounds and said that this hydroxy group (identified as OR_4) was "critical" in distinguishing over the '902 patent compounds. PFF ¶¶ 397-98.

Mylan tries to argue that intramolecular hydrogen binding in olmesartan eliminates this critical structural difference and makes olmesartan's hydrophilic alcohol act like a lipophilic alkane. PFF ¶¶ 399-400. Regardless of the merits of this argument in terms of structural difference, Dr. Weinstock admitted that, if intramolecular hydrogen bonding does in fact occur in olmesartan, it would "form a ring" around the 4- and 5-positions and, as a result, olmesartan "would certainly differ in structure from losartan, EXP 3174 and the '902 patent compounds" by virtue of this new ring. PFF ¶¶ 401-02.

At the 5-position, olmesartan medoxomil and the '902 patent compounds also differ significantly. Olmesartan medoxomil has a carboxylic acid group linked to a medoxomil ester to form a prodrug. PFF ¶¶ 501-503. None of the '902 patent examples is a prodrug, like olmesartan medoxomil. In fact, examples 1, 3, 4, and 5 of the '902 patent have an aldehyde at the 5-position which is not a carboxylic acid group, and cannot form a prodrug. PFF ¶ 385.

Agere Sys. v. Advanced Envtl. Tech. Corp., No. 02-3830, 2008 U.S. Dist Lexis 91887, at *48 n.21 (E.D. Pa. Aug. 18, 2008) (interrogatory responses "not binding"; findings conformed to proof at trial).

Indeed, when DuPont later attempted to use medoxomil to make prodrugs of the '902 patent compounds it did not work, demonstrating the significant difference in overall structure between the '902 patent compounds and olmesartan medoxomil. PFF ¶ 529.

3. Mylan Failed To Prove Motivation To Make The Specific Modifications Necessary To Achieve Olmesartan Medoxomil

Assuming, contrary to the proof at trial, that one of ordinary skill in the art would have selected one of the '902 patent compounds as a lead, Mylan must next prove that an ordinary researcher would be motivated to make the specific modifications to the '902 patent compounds necessary to create olmesartan medoxomil. *Eisai Co.*, 533 F.3d at 1359 (citing *KSR*, 127 S. Ct. at 1742); *Takeda Chem. Indus.*, 492 F.3d at 1355. The absence of a motivation to modify is dispositive in an obviousness determination. *See Gambro Lundia AB v. Baxter Healthcare Corp.*, 110 F.3d 1573, 1578-79 (Fed. Cir. 1997).

Here, the evidence at trial proved that even had one started with the '902 patent compounds, there was no motivation to make the modifications necessary to get to olmesartan medoxomil. PFF ¶¶ 416-532. None of the skilled scientists at dozens of companies working in the ARB field before April 26, 1991 who collectively synthesized thousands of different ARB compounds -- not even DuPont -- made the modifications that Mylan now suggests would have been readily apparent to an ordinary researcher.

a. There Are Many Thousands Of Reasonable Modifications To The '902 Patent Compounds

Even using the '902 patent compounds as leads, a medicinal chemist of ordinary skill would have had thousands of possible and scientifically reasonable replacements available at different positions, none of which would result in olmesartan medoxomil. PFF ¶ 420 ("THE COURT: Well, if that's true, isn't that true also when you take a particular lead like '902, you could go in many different directions? THE WITNESS: Absolutely."); *see also* PFF ¶ 418

("[T]here are all kinds of other options"). For example, the imidazole ring itself, positions 2, 4 and 5 of the imidazole ring, the biphenyl group and the tetrazole group all could be subject to many possible modifications. PFF ¶ 419. Indeed, companies working on ARBs at the time actually made structural modifications to each one of those positions on losartan. PFF ¶¶ 421. Dr. Yanagisawa's testimony about the thousands of different possible compounds that could be made from the many imaginable synthetic routes was unchallenged.[14] PFF ¶ 419. At trial, Mylan identified nothing in the prior art that would restrict the thousands of possible changes and direct a person of ordinary skill to make the specific modifications necessary to create olmesartan medoxomil. An invention is not obvious when "thousands and thousands of permutations and paths" face the ordinary researcher. *AstraZeneca AB v. Mylan Labs., Inc.*, 490 F.Supp 2d 381, 457 (S.D.N.Y. 2007).

b. There Was No Motivation To Modify The 4-Position To Hydroxyisopropyl, Or Even To An Alcohol Group

An ordinary medicinal chemist, starting with the '902 patent, likely would have left the 4-position intact, because that is what distinguished the '902 patent compounds from losartan and presumably accounted for their improved activity.[15] PFF ¶ 429. If that ordinary researcher did choose to modify the 4-position, the researcher would have been likely to follow the '902 patent's teachings that an alkyl, a lipophilic hydrocarbon of the alkane class, worked

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14 Mylan hinted at an argument that the motivation to modify was based on Daiichi Sankyo's desire to obtain a patent. However, under Federal Circuit caselaw, the person of ordinary skill is not permitted to invent and the innovator's motivation is irrelevant. *Life Tech., Inc. v. Clontech*, 224 F.3d 1320, 1325 (Fed. Cir. 2000).

15 Mylan has offered no logical reason why a researcher would begin with the '902 patents, the supposed advantages of which are provided by the lipophilic alkyl groups, only to discard the very features that provided the advantage. PFF ¶ 143. *Eisai Co.*, 533 F.2d at 1388 (no obviousness when the record "show[ed] no discernible reason for a skilled artisan to begin with [a lead] only to drop the very feature that gave this advantageous property [for which lead was selected]").

well. PFF ¶¶ 428, 430. Hundreds of reasonable substitutions along these lines were possible, just staying within the alkane class or other classes of lipophilic hydrocarbons (alkenes or alkynes). PFF ¶¶ 432-38. In fact, Dr. Weinstock admitted that modifying an alkyl group to form other alkanes, alkenes, or alkynes was exactly what an ordinary medicinal chemist starting with an alkyl group would do. PFF ¶¶ 431. Given that the '902 patent itself taught the benefits of a lipophilic group at the 4-position, there would have been ***no*** motivation to try a class with opposite properties – such as the hydrophilic alcohols.[16] PFF ¶¶ 439-43.

c. The Dupont SAR Taught Away From Making The 4-Position Hydrophilic

As demonstrated above, the DuPont SAR and the rest of the prior art taught that a lipophilic substituent was preferred at the imidazole 4-position, in order to provide best activity. Accordingly, a person of ordinary skill in the art would not have been motivated to modify the 4-position of the '902 patent compounds to create olmesartan medoxomil, which has a hydrophilic hydroxyisopropyl group at its 4-position. The art taught exactly the opposite. PFF ¶¶ 441-42.

Recently, the Federal Circuit affirmed the non-obviousness of a chemical compound when the prior art taught a preference for substituents with opposite properties. *Eisai Co.*, 533 F.3d at 1355. In *Eisai*, the prior art taught that lipophilicity at a particular position on a ring structure conferred beneficial results. *Id.* at 1357. The invention at issue in *Eisai* replaced a ***more*** lipophilic substituent with a ***less*** lipophilic substituent, defying the prevailing SAR and the Federal Circuit held that the invention was not obvious. *Id.* at 1355; *see also Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 364 F. Supp. 2d 820, 902 (S.D. Ind. 2005) ("Where the prior art 'teaches away' from the claimed invention rather than motivating a person of ordinary skill in

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16 Even if a person of ordinary skill in the art, for some unknown reason, considered replacing the 4-position of the '902 patent compounds with an alcohol, he would not have likely turned to hydroxyisopropyl -- a very rare substituent. PFF ¶ 443.

the art to do what the patentee has done, the claimed invention is nonobvious."), *aff'd*, 471 F.3d 1369 (Fed. Cir. 2006). *Eisai* is on all fours with this case.

At trial, Mylan attempted to avoid this point by arguing that, at the receptor site, olmesartan's normally hydrophilic hydroxyisopropyl acts as if it is lipophilic based on intramolecular hydrogen bonding. PFF ¶¶ 399. Dr. Weinstock, however, admitted that he came up with this theory by ***starting*** with the structure of olmesartan and applying his 50-plus years of experience -- none of which would have been available to one of ordinary skill in April 1991. PFF ¶¶ 405, 444. Dr. Weinstock also admitted that there was no suggestion of intramolecular hydrogen bonding in any of the pre-1991 ARB literature and an ordinary medicinal chemist could not have predicted that intramolecular hydrogen bonding would occur at the receptor site. PFF ¶¶ 404, 445-48, 452. Dr. Weinstock further admitted that he had no literature or experimental support for his theory that intramolecular hydrogen bonding would transform the hydrophilic hydroxyisopropyl to lipophilic. PFF ¶¶ 403-404, 406. And, in fact, this idea of "transformation" is simply wrong -- as Dr. Lipinski explained, an intramolecular hydrogen bond would make the 4-position oxygen even more hydrophilic. PFF ¶ 407.

Instead of prior art, Mylan's argument relies impermissibly on post-invention papers by the inventors of olmesartan medoxomil, authored years after the invention (*e.g.*, PTX 26 and DTX 77), which offer theories on possible explanations for olmesartan medoxomil's test results and unexpectedly good activity. The intramolecular hydrogen bonding theory was described by the inventor-author himself as "speculation." PFF ¶¶ 409-11. And, Mylan's experts admitted that these attempts at post-invention rationalizations would not have been possible before olmesartan medoxomil was made and tested and, in any event, exceeded the predictive capabilities of ordinary researchers at the time. PFF ¶¶ 409, 446, 451-52. Mylan's

intramolecular hydrogen bonding theory is exactly the kind of hindsight analysis that is "always inappropriate" in assessing obviousness. *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, at 1364 (Fed. Cir. 2008); *see also KSR*, 127 S. Ct. at 1742.

In any event, even if intramolecular hydrogen bonding does transform the normally hydrophilic hydroxyisopropyl at the 4-position of olmesartan to lipophilic, that would in itself be an invention. As Dr. Lipinski testified, an ordinary medicinal chemist would not have thought to use a hydrophilic group in a situation that called for a lipophilic group, hoping that some transformation might occur -- "that would be pretty inventive." PFF ¶ 412. The Supreme Court defined obviousness as the "*predictable* use of prior art elements according to their *established* functions" -- to use the normally hydrophilic hydroxyisopropyl as a lipophilic substituent -- would certainly be unpredictable and non-obvious. *KSR* 127 S. Ct. at 1740 (emphasis added); *In re Gordon*, 733 F.2d 900 (Fed. Cir. 1984) (no obviousness when use of component is opposite to its usual function).

d. Bioisosterism And The "Principle Of Minor Modifications" Provide No Motivation To Modify The '902 Patent Compounds To Obtain Olmesartan

Dr. Weinstock cited "bioisosterism" and a so-called "principle of minor modifications" as supposed motivations to modify the 4-position to a hydrophilic alcohol. However, the modifications proposed by Dr. Weinstock are neither modern bioisosteric replacements nor minor modifications. PFF ¶¶ 453-54. In addition, both theories lead to thousands of possible modifications with neither theory a predictor of improved activity (PFF ¶¶ 484, 485, 489, 497-500) -- this is certainly not an example of the "finite number of identified predictable solutions" needed for obviousness under *KSR*.

i. Bioisosterism Provides No Motivation

To support his bioisosterism theory, Dr. Weinstock relied on an outdated concept of "classical isosteres" from the 1920s (matching groups based only on number of outside electrons). PFF ¶¶ 457-459. By at least the 1970s, "classical isosteres" had been recognized to be of little use in drug research (which emphasizes biological and chemical properties), including by the very Thornber reference on which Mylan relies. PFF ¶¶ 461-70.

Under modern bioisosterism theory, practiced since the 1970s, according to the Thornber reference, researchers look to various chemical and biological parameters to match groups as possible replacements. PFF ¶¶ 768-73. Applying the modern bioisosteric analysis to the '902 patent compounds revealed that Mylan's proposed modifications would not be modern bioisosteric replacements. PFF ¶¶ 474-476. Further, the Thornber reference used a simple ring structure as an example to demonstrate the "vast number of permutations" possible using bioiosteric replacements -- more complicated structures, such as the '902 patent compounds, would yield a "much, much larger" number of permutations, as nearly every position of the imidazole ring may be substituted. PFF ¶ 485. This is far from the easily traversed, small and finite number of alternatives that *KSR* suggested might support an inference of obviousness. *Ortho-McNeil*, 520 F.3d at 1364.

Additionally, bioisosterism, as Dr. Weinstock admitted, is "not [a] predictor" or a "guarantee" -- "without some SAR . . . it would be difficult to anticipate what . . . result you would get." PFF ¶ 489. Here, existing SAR would have taught away from the substitution of a hydroxyalkyl for the '902 patent compounds' alkyls. PFF ¶¶ 486-87.

ii. The "Principle Of Minor Modification" Provides No Motivation

Likewise, a person of ordinary skill in the art would not have modified the 4-position of the '902 patent compounds to reach olmesartan medoxomil using the so-called "principle of minor modifications" from Wermuth's "philosophy" paper. PFF ¶ 490. This chemistry philosophy paper published in an obscure French journal in 1966 describes "the whole range of modifications that are possible in medicinal chemistry" with no guidance. PFF ¶¶ 490-92. The "minor modifications" suggested by Wermuth are "actual reactions" that are "simple and easy to do" directly with known starting materials. PFF ¶ 493. Dr. Weinstock admitted that his proposed "hydroxylation" and "methylation" modifications were not real reactions to be applied directly to the '902 patent compounds, but rather only "conceptual," and thus not "minor modifications" under Wermuth. PFF ¶¶ 490-96. Moreover, even if one could extend Wermuth's principle to "conceptual" modifications, Wermuth provides no way to distinguish between different modifications or locations for modifications, leaving a medicinal chemist with "thousands and thousands" of possibilities starting with the '902 patent compounds. PFF ¶¶ 497-99. Finally, as Dr. Weinstock admitted, Wermuth suggests that minor modifications can lead to "surprising" results, not "predictable" solutions required by *KSR*. PFF ¶ 500.

e. Mylan Has Not Proved Any Motivation To Modify The 5-Position As In Olmesartan Medoxomil

The trial record demonstrates that one of ordinary skill in the art would not have been motivated to modify the 5-position of any of the '902 patent compounds to obtain a carboxylic acid with a medoxomil promoiety. PFF ¶¶ 501-32. First, while a carboxylic acid was known as a possibility for the 5-position, as Dr. Weinstock admitted, it was associated with poor oral absorption, a problem for which the prior art offered no predictable solutions. PFF ¶¶ 501-02, 504-05. In fact, two of the three preferred examples of the '902 patent contain an aldehyde at

the 5-position, suggesting an aldehyde may be more advantageous than a carboxylic acid. PFF ¶ 502.

Second, a person of ordinary skill in the art would have had no motivation to modify the 5-position of the '902 patent compounds to use a medoxomil prodrug approach. It is difficult to design a prodrug because "there are a whole series of hurdles that you have to overcome." PFF ¶¶ 508-13. As Mylan's Dr. Hieble admitted, even today, pharmaceutical companies "avoid prodrugs" because "there are problems in . . . determining whether the prodrug itself has pharmacology" and "whether the conversion of the prodrug to [the] active [form] is reproducible. It can be variable." PFF ¶ 531. Creating a prodrug in April 1991 was a "last resort," "a desperation, last-ditch approach" which was "unpredictable." PFF ¶ 530-31.

Third, a medicinal chemist of ordinary skill could not predict ahead of time which, if any, promoiety would work. PFF ¶¶ 513-15. Hundreds of possible promoieties could be tried with olmesartan, at each of three possible positions. PFF ¶¶ 516-18. Among the possible promoieties, nothing pointed to medoxomil, which by all accounts is infrequently used.[17] While a medoxomil moiety had been used with other drug classes, a group that works for one structure may not work for another. PFF ¶¶ 514, 516-18. Indeed, in 1994, DuPont tried to make a medoxomil prodrug of Example 2 of the '902 patent and it failed -- resulting in a 3-fold ***decrease*** in activity. PFF ¶ 529.

In addition, of all the promoeities tried, only a medoxomil ester at the 5-position led to a compound with enhanced oral activity that also would crystallize (PFF ¶¶ 519, 525) -- crystallization is an "important factor in [a drug's] manufacturing, its formulation and in quality

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[17] PFF ¶ 526 (Dr. Hieble: Prior to this litigation you never heard of using a medoxomil as an ester to make a prodrug. Right? A. Not that specific ester, no.); (Dr. Fink: I had to Google medoxomil when I first heard about olmesartan medoxomil. I seriously never heard of it.").

assurance." PFF ¶¶ 520-21. A medicinal chemist of ordinary skill in April 1991, and even today, cannot predict before making a prodrug whether it will crystallize. PFF ¶¶ 522-24.

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In sum, the evidence revealed a thicket of thousands of possible modifications at all positions, none predictable, with the only clear paths leading away from olmesartan medoxomil. This is the antithesis of obviousness.

4. Mylan Failed To Prove Any Reasonable Expectation Of Obtaining Olmesartan Medoxomil's Unique Combination Of Properties

To satisfy the next element of its defense, Mylan must prove by clear and convincing evidence that a person of ordinary skill in the art would have had a "reasonable expectation of success in choosing the '902 patent compounds as leads and modifying them to reach olmesartan medoxomil." Success is not just some "baseline activity," rather, Mylan must prove by clear and convincing evidence that an ordinary medicinal chemist could have reasonably expected the "most desirable combination of pharmacological properties" that olmesartan medoxomil possesses. *Yamanouchi*, 231 F.3d at 1345; *see Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.*, 348 F. Supp. 2d 713, 752 (N.D.W.Va. 2004), *aff'd*, 161 Fed. Appx. 944 (Fed. Cir. 2005) (reasonable expectation of success requires "sufficient teaching in the prior art to indicate that the end product is reasonably likely to exhibit the patented invention's unique combination of properties."). This is because "[f]rom the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing." *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963).

Researchers at Daiichi Sankyo discovered olmesartan medoxomil's surprisingly high activity in binding affinity tests and when administered intravenously and orally. In binding affinity, olmesartan is about 470 times more potent than losartan; in intravenous activity,

olmesartan is about 40 times more potent than losartan; and, olmesartan medoxomil shows a 100-fold increase in oral potency over losartan. PFF ¶ 544.

A person of ordinary skill in the art could not have predicted the remarkably superior potency of olmesartan medoxomil. Dr. Weinstock considered lesser improvements in binding affinity (11 times) and oral activity (20 times) in the DuPont work to be "very remarkable" and "a big breakthrough." PFF ¶¶ 548; *see also* 551, 547 ("virtually impossible to predict this change in potency, even an increase, but much less the quantity"). In April 1991, as Mylan's experts admitted, the ARB art was unpredictable. PFF ¶¶ 537-43. Indeed, Dr. Weinstock admitted that "making a change will affect the properties of the compound in many ways, and a simple change will often affect properties in different ways than another simple change because we're dealing with several properties at once." PFF ¶ 550. Even adding one tiny hydrogen atom to the imidazole of an ARB can result in "very, very different properties," said Dr. Weinstock. PFF ¶ 550. "To the extent an art is unpredictable, as the chemical arts often are . . . potential solutions are less likely to be genuinely predictable." *Eisai Co.*, 533 F.3d at 1359.

Moreover, the results achieved with olmesartan medoxomil would have been impossible to predict because the prior art taught that lipophilicity at the 4-position was needed for the best binding to the receptor and hydrophilicity was discouraged as decreasing oral activity. A medicinal chemist of ordinary skill reasonably would have expected that olmesartan's hydrophilic group at the 4-position would result in a compound with ***decreased*** binding and ***decreased*** oral activity compared to losartan, ***not*** olmesartan medoxomil's superior properties. PFF ¶¶ 552-56. Indeed, inventor Dr. Yanagisawa was quite surprised with his results. PFF ¶¶ 42, 51, 286. So were others. When asked whether, prior to April 1991, DuPont had ever considered what Mylan says was obvious -- modifying the '902 patent compounds to

use a hydroxyalkyl group at the 4-position -- the DuPont project leader Dr. Timmermans explained that DuPont had not. PFF ¶ 557. He explained that, at that time, it would have been "counterintuitive" to do so because, according to DuPont's work, lipophilicity at the 4-position yielded "good binding" and "better oral bioavailability." PFF ¶ 557. In the words of the Supreme Court, there can be no "predictable solution" -- and thus no obviousness -- when the art teaches away from the invention. *KSR,* 127 S. Ct. at 1740. This is just such a case.

D. The Objective Indicia Support A Finding Of Non-Obviousness

Objective indicia are "essential and integral" to obviousness, and must "be considered as part of all the evidence, not just when the decision maker remains in doubt after reviewing the art." *Alco Standard Corp. v. Tennessee Valley Auth.*, 808 F.2d 1490, 1498 (Fed. Cir. 1986); *Demaco Corp. v. F. Von Langsdorff Licensing, Ltd.*, 851 F.2d 1387, 1391 (Fed. Cir. 1988). They "may often establish that an invention appearing to have been obvious in light of the prior art was not." *Demaco*, 851 F.2d at 1391.

Objective indicia of non-obviousness include: (i) unexpected results, (ii) commercial success, (iii) long felt, unmet need, (iv) copying, and (v) industry praise and recognition for the invention. *Graham v. John Deere Co.*, 383 U.S. at 17. Importantly, they are not limited to what was known at the time of the invention, but include later discovered unexpected properties of the invention. *Knoll Pharm. Co., Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004).

1. Unexpected Results

In both pre-clinical testing and human clinical trials, overwhelming evidence shows that olmesartan medoxomil exhibits remarkable and unexpected properties in relation to

the '902 patent compounds and to commercially available ARBs. PFF ¶¶ 673-78.[18] Any one of these unexpected properties would be sufficient to demonstrate objectively that the claimed invention was not obvious. That it has all of these unexpected properties is truly remarkable and unexpected.

a. Olmesartan Medoxomil Demonstrates Remarkable Pharmacological Properties

The simple fact is that for ***every*** assay where olmesartan was compared to the '902 patent compounds, olmesartan had ***better*** properties. Mylan points to nothing to the contrary.

i. Greater *In Vivo* And Oral Potency

Mylan's Dr. Hieble admitted potency is "very important." PFF ¶¶ 572-73, 588-89. The experts agree that the '902 patent makes clear that if a compound has 2- to 4-fold better potency, then that difference in activity is remarkable and unexpected.[19] PFF ¶¶ 558-59. Here, the claimed invention was two times more potent than the '902 patent compounds when tested *in vivo*, and was three times more potent than those compounds when tested orally. PFF ¶¶ 584-86, 591.[20] It was approximately 40 times more potent than losartan. PFF ¶¶ 584, 592. Thus, olmesartan medoxomil has potency that is unexpected compared to the '902 patent compounds, and to the gold standard at the time, losartan. PFF ¶¶ 587, 593-94

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18 Non-human pharmacological testing results are sufficient to demonstrate unexpected results. *Eli Lilly and Co. v Zenith Goldline Pharms., Inc.*, 364 F. Supp. 2d 820, 908 (S.D. Ind. 2005), *aff'd*, 471 F.3d 1369 (Fed. Cir. 2006).

19 Mylan's expert Dr. Hieble's standard for unexpected properties was unsupported by the literature and grounded solely on his personal experience at GSK for selecting a compound to be developed commercially. PFF ¶¶ 560-62.

20 Dr. Hieble's assertion that one could not rely on these differences in potency because of the "inherent variability" in the assays used was unsupported and not credible. PFF ¶¶ 574-83, 590.

ii. Fewer Drug-Drug Interactions

Drug-drug interactions are "an extremely common reason" for the removal of a commercial drug from the market, and represent a "serious event" -- "people can die." PFF ¶¶ 607-08. Olmesartan medoxomil is four- to seven-fold less likely to inhibit liver enzymes than the '902 patent compounds, thus reducing the risk of such interactions. PFF ¶¶ 612-13.[21] Dr. Hieble agreed that the difference between olmesartan and Examples 2 and 6 was substantial and unpredictable. PFF ¶¶ 613-14. Olmesartan medoxomil's substantially lower likelihood of drug-drug interactions in comparison to commercial ARBs and the '902 patent compounds was unexpected. PFF ¶¶ 614-15.

iii. Insurmountable Antagonism

Insurmountable antagonism is important because "a drug that exhibits insurmountable antagonism should, in general, have a longer effect in patients." PFF ¶ 596; *see also* PFF ¶ 597. Dr. Hieble agreed olmesartan medoxomil is an insurmountable antagonist, and, in contrast, at the same concentration tested, example 6 of the '902 patent is not. PFF ¶ 598. Olmesartan medoxomil's insurmountable antagonism is an entirely unexpected property. PFF ¶ 600.

iv. Inverse Agonism

Inverse agonists might benefit patients who have low levels of renin and in treating cardiac hypertrophy. PFF ¶¶ 601-03. Dr. Hieble admitted that olmesartan medoxomil has higher inverse agonist activity than example 6 of the '902 patent compounds, which was

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[21] Dr. Hieble argued that there is a 30 micromolar "cut off" where any compound that has an IC_{50} value above that would have no clinically relevant drug-drug interactions. That cut-off, however, is arbitrary and without factual basis. PFF ¶¶ 609-10. Indeed, losartan's IC_{50} value is about 40 and its drug-drug interactions "are mentioned on the labeling" and "may be a concern to practicing physicians." PFF ¶ 611.

unpredictable. PFF ¶¶ 604-05. Olmesartan medoxomil's superior inverse agonist properties over example 6 is an unpredictable and unexpected property. PFF ¶ 605.

v. Greater Selectivity

Dr. Hieble testified that selectivity is "very important" because "you don't want other off target activities which could . . . give rise to side effects . . . ." PFF ¶ 618; see also PFF ¶¶ 616-17.[22] Olmesartan medoxomil is at least 12.5-fold more selective than losartan. PFF ¶¶ 619. Olmesartan medoxomil's excellent selectivity is unexpected. PFF ¶ 620.

b. Olmesartan Medoxomil Demonstrates Remarkable Efficacy And Clinical Pharmacological Properties

i. Superior Blood Pressure Lowering Ability

Mainstream physicians "focus on [the agents'] ability to lower blood pressure because … the evidence is very strong that lowering blood pressure lowers risk." PFF ¶ 621; *see also* PFF ¶¶ 622-24; PFF ¶ 625 ("THE COURT: And the reason doctors would prescribe it is because, generally speaking, high blood pressure is a higher risk than lower blood pressure. THE WITNESS: Yes."). Reducing blood pressure by as little as a few millimeters of mercury significantly reduces the risk of a fatal coronary event. PFF ¶¶ 626-30. And, given the strong correlation between high blood pressure and cardiovascular risk, blood pressure lowering ability is the predominant criterion that practicing physicians in the U.S. use to select anti-hypertension agents. PFF ¶¶ 621, 631.

Olmesartan medoxomil's superior blood pressure lowering ability over other ARBs is unexpected. PFF ¶¶ 642, 653. Peer-reviewed articles demonstrate that olmesartan medoxomil is significantly better at lowering blood pressure than other commercially available

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[22] To the extent Mylan's Dr. Brown incredulously testified that potency and selectivity are not important, that was directly contradicted by Mylan's Dr. Hieble (and Daiichi Sankyo's experts). PFF ¶¶ 572-73, 618.

ARBs: "Among the studied ARBs, olmesartan can reduce diastolic blood pressure and systolic blood pressure significantly more than other ARBs." PFF ¶¶ 647; *see also* PFF ¶¶ 642-49, 651. Mylan's Dr. Brown agreed, and gave olmesartan medoxomil his ***highest ranking*** among ARBs for its blood pressure lowering efficacy. PFF ¶ 650.[23]

ii. Olmesartan Is At The Top Of All ARBs For Its Clinical Pharmacological Properties

Olmesartan medoxomil's unexpected pharmacological properties are not limited to assays conducted on animals. There is little dispute that it has superior ***clinical*** pharmacological properties in humans compared to commercial ARBs.

Mylan's Dr. Brown provided a chart ranking the commercial ARBs for various clinical pharmacological properties, including duration of action, drug interaction, food interaction, selectivity, accumulation and potency. PFF ¶¶ 654-55. Under Dr. Brown's own ranking system, he gave olmesartan medoxomil the ***highest score*** for each of those properties (some other ARBs had the same score for some properties). PFF ¶ 655. Dr. Carey agreed with those rankings. PFF ¶ 655. In fact, Dr. Brown admitted that under his ranking system "***no other ARB is given the highest score*** from 1 to 5 for all of those properties." PFF ¶ 655. Plainly, that is remarkable and unexpected. PFF ¶ 656.

iii. Mylan Does Not Seriously Dispute Olmesartan Medoxomil's Unexpected Properties

As noted above, Mylan's Dr. Brown admitted that olmesartan medoxomil is either the best or among the best commercial ARBs for every key "clinical consideration," other than outcome-related categories. But at trial Mylan asserted that olmesartan medoxomil's lack of

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[23] In contrast, since the '902 patent compounds never reached the clinical trial stage, undoubtedly they would have been scored a zero under Dr. Brown's ranking system. PFF ¶ 652.

"outcome studies" trumps the overwhelming evidence of unexpected and remarkable results.[24] The evidence at trial belied that contention.

While "outcome data are valuable for sure . . . they're only one part of the equation that physicians should use when deciding to use any hypertensive agent, and there are many other factors that go into it." PFF ¶ 632; *see also* PFF ¶ 633.[25] Indeed, over 58 million prescriptions have been written for the BENICAR® family of products without any outcome data whatsoever. PFF ¶ 634. Mylan's own witness, Dr. Cohn, admitted -- outside the context of this litigation -- that outcome studies are not particularly relevant to the practicing physician. Dr. Cohn wrote: "[t]he painful truth is that . . . large scale morbidity/mortality [outcome] trials . . . are ***unlikely to help the practicing physician*** decide how to treat an individual patient with hypertension." PFF ¶ 641 (emphasis added); *see also* PFF ¶¶ 638-40.

c. Properties In Addition To Lowering Blood Pressure

In addition to lowering blood pressure better than other ARBS, olmesartan medoxomil has been shown to provide other benefits that are unexpected. PFF ¶¶ 657, 660, 664, 668, 672. Four particularly important ones were highlighted at trial: (1) increasing renin secretion, (2) reducing atherosclerotic plaque volume, (3) reversing diabetic kidney disease, and (4) reversing artery damage:

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24 Mylan's reliance on the FDA "warning" letter is misplaced. That letter simply stated that to the extent there are head-to-head clinical trials comparing BENICAR® to other ARBs, those trials were not designed to compare maximum doses, and instead primarily compared starting doses. PFF ¶ 740. But even Mylan's Dr. Cohn testified that those "starting dose" trials support a claim that "a starting dose [of olmesartan] may actually produce a greater benefit on blood pressure lowering than the starting doses of the other drugs." PFF ¶ 651; *see also* PFF ¶ 741.

25 Neither the FDA nor the USPTO require outcome studies -- which can cost upwards of one hundred million dollars and take years to complete. PFF ¶¶ 635-37.

- Increasing renin secretion: olmesartan medoxomil increases renin secretion significantly more than other ARBs to provide the highly desirable effects of stimulating the AT_2 receptor. PFF ¶¶ 616-17, 658-59.

- Reducing plaque volume: olmesartan medoxomil not only significantly reduces plaque volume, but actually reverses plaque volume towards normal in patients with atherosclerosis; and no other ARB has been shown to have this property. PFF ¶¶ 661-63.

- Reversing kidney disease: olmesartan medoxomil significantly reverses damage to kidney tissue in animal studies. PFF ¶¶ 665-67.

- Reversal of vascular damage: olmesartan medoxomil "literally reverse[d] the fundamental damage which occurs in small vessels" from hypertension, causing a "reduction in wall-to-lumen ratio . . . back to the level of [a] healthy normal control." PFF ¶¶ 669-70. No other ARB has demonstrated this ability to reverse artery damage. PFF ¶ 671.

* * *

In sum, Mylan has failed to meet its burden of proving by clear and convincing evidence that one of ordinary skill in the art would have predicted the unique and remarkable properties of olmesartan medoxomil, whether each is taken alone or in combination -- it "is a very special compound." PFF ¶ 678; *see also* PFF ¶¶ 673-77.

2. Commercial Success

Commercial success is "usually shown by significant sales in a relevant market." *Ecolochem, Inc. v. Southern Cal. Edison Co.*, 227 F.3d at 1361, 1377 (Fed. Cir. 2000). As one court noted: "If the patented drug were not a commercial success, generic manufacturers would have little interest in offering their own versions of the drug." *Eli Lilly & Co. v. Zenith Goldline Pharms.*, No. IP 99-38-C, 2001 U.S. Dist. LEXIS 18361, at *36 (S.D. Ind. Oct. 12, 2001). That is, if Benicar were ***not*** a commercial success, Mylan never would have challenged the patent.

a. BENICAR® Is An Unqualified Commercial Success

By every conceivable metric, the BENICAR® family of products is a commercial success -- indeed, it is a blockbuster. PFF ¶¶ 679-82. The BENICAR® family's gross sales were $1.3 billion in 2008, and to date total over $4 billion. PFF ¶ 683; *see also* PFF ¶¶ 684-86.

BENICAR®'s success exceeded even Daiichi Sankyo's own optimistic pre-launch sales forecasts. PFF ¶¶ 691-92. Cumulative net sales are nearly ***double*** Daiichi Sankyo's pre-launch predictions. PFF ¶¶ 693-95.[26]

Despite being the seventh, and last, entrant to a crowded market with entrenched competitors, BENICAR®'s market share has grown to over 16.6%, making it the third largest in terms of market share. PFF ¶¶ 687; *see also* PFF ¶¶ 689-90.[27] Mr. Boghigian testified that his own trend line for BENICAR® -- when corrected to remove the errant zeros for years when BENICAR® had not yet come to market -- is "similar" to the "extremely nice growth curve" for DIOVAN®, the market leader. PFF ¶ 688.

b. Commercial Success Is Attributable To BENICAR®'s Properties

Mylan's principal assertion was that BENICAR®'s success is due not to olmesartan medoxomil's remarkable properties, but rather to marketing. Mylan's attempt to divorce BENICAR®'s commercial success from the attributes of the product must fail.

Mylan's Mr. Boghigian admitted that all pharmaceutical companies engage in marketing, but even with significant marketing, "there's no guarantee[] of success with a product." PFF ¶¶ 714, 722. That is because the marketing is "aimed at creat[ing] awareness"

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26 Despite Mylan's incessant quibbling, the evidence at trial demonstrated that BENICAR® is hugely profitable. Both sides' experts agree that the cumulative net income earned by Daiichi Sankyo from the BENICAR® franchise exceeded $715 million by 2007 alone. PFF ¶¶ 698-99; *see also* PFF ¶¶ 700-02.

27 That Benicar was last to market makes its rise in sales and use even more remarkable. PFF ¶¶ 703-12.

and promoting the characteristics of the product. PFF ¶¶ 717-18; *see also* PFF ¶¶ 719-21.[28] Thus, ultimately the success of a drug will be determined by its properties. PFF ¶ 713.

Moreover, marketing can at best get a physician to try a drug once. PFF ¶ 725. If the drug does not live up to the marketing message or the physician's expectations, he or she will not prescribe it again. PFF ¶¶ 723-35. Based on their patients' positive experiences, doctors have consistently rated BENICAR® the best ARB or among the best ARBs. PFF ¶ 726. The Federal Circuit recognized this very point in *Hybritech, Inc. v. Monoclonal Anti-Bodies, Inc.*, 802 F.2d 1367, 1382 (Fed. Cir. 1986) noting that that advertising "does not make these potential users buy them; the products have to work."[29]

In sum, nothing in the record explains the extraordinary commercial success of BENICAR® ***other*** than the fact that physicians prescribe it because it works extraordinarily well.

3. Long-felt, Unmet Need

Long-felt need is a result of the failure of others to solve a problem and meet a real, commercial demand. CHISUM ON PATENTS, § 5.05. S*ee also, e.g., Eli Lilly & Co. v. Premo Pharm. Labs.*, No. 78-2589, 1979 U.S. Dist. LEXIS 11039 (D.N.J. July 13, 1979) (finding a drug nonobvious despite its structural similarity to previously developed drugs because it solved problems associated with previous drugs). The fact that other "major players" in a field were

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28 Moreover, Daiichi Sankyo did not spend an inordinate amount on marketing. PFF ¶ 727. Rather, its marketing efforts were proportional to, and in many cases substantially lower than, those of its competitors. PFF ¶¶ 728-32.

29 The FDA "warning" letter did not have any substantial effect on BENICAR®'s commercial success. Five of the other six ARB companies received similar letters. PFF ¶¶ 738-39. Nevertheless, sales of the BENICAR® franchise continued to increase and physicians continued to rate BENICAR® the best or among the best among ARBs even after the warning letter and the various corrective measures the FDA required of Daiichi Sankyo. PFF ¶¶ 742-46.

attempting (and failing) to meet the need at the same time as the inventor is strong evidence of nonobviousness. *See Minnesota Mining and Manufacturing Co. v. Johnson Orthopaedics, Inc. and Johnson*, 976 F.2d 1559, 1574-1575 (Fed. Cir. 1992); *In re Dow Chemical Co.*, 837 F.2d 469, 472 (Fed. Cir. 1988) ("Recognition of need and difficulties incurred by those skilled in the field, are classical indicia of nonobviousness.").

As Mylan's Dr. Cohn testified at trial, in 1991 there was a "great" and "unmet" need for better drugs to treat hypertension more effectively without "terrible" side effects. PFF ¶ 747. Thousands of compounds were made to try to fulfill that need. PFF ¶ 748. At that time, losartan had just entered the clinical trials and no one knew whether it would be efficacious and free of side-effects in humans. PFF ¶ 749. Even if losartan turned out to be successful, the need would exist for better, more potent ARBs. PFF ¶ 750. BENICAR® clearly met the need that existed at the time of the invention. PFF ¶¶ 751-52.

4. Mylan Copied The Claimed Invention

It is undisputed that Mylan's ANDAs copied the claimed invention. Mylan could have simply waited for the olmesartan patent to expire, but instead chose to copy each of the three products in the BENICAR® family. PFF ¶¶ 753-55.

5. Industry's Praise And Recognition For Benicar

The industry recognized BENICAR's achievements. Dr. Yanagisawa received a prestigious award from the Pharmaceutical Society of Japan for his work on olmesartan medoxomil. PFF ¶ 756.

CONCLUSION

For the foregoing reasons, based on the evidence that was admitted at the trial of this action, final judgment should be entered in favor of Daiichi Sankyo.

Respectfully Submitted,

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By: S/William J. Heller

William J. Heller
McCARTER & ENGLISH, LLP
Four Gateway Center
100 Mulberry Street
Newark, New Jersey 07102
TEL: (973) 622-4444

Of Counsel:

Lisa B. Pensabene
Dominick A. Conde
Joshua I. Rothman
FITZPATRICK, CELLA, HARPER & SCINTO
30 Rockefeller Plaza
New York, New York 10112
TEL: (212) 218-2100

Henry B. Gutman
Robert A. Bourque
Noah M. Leibowitz
SIMPSON THACHER & BARTLETT LLP
425 Lexington Avenue
New York, New York 10017
TEL: (212) 455-2000

Attorneys for Plaintiffs
Daiichi Sankyo Company, Limited and
Daiichi Sankyo, Inc.

CERTIFICATE OF SERVICE

The undersigned hereby certifies that the foregoing document was caused to be served on May 1,2009, via ECF and email upon the following:

Arnold B. Calmann
Jeffrey Soos
Katherine A. Escanlar
SAIBERLLC
One Gateway Center, 13th Floor
Newark, New Jersey 07102-5311

David J. Harth
Melody K. Glazer
PERKINS COIE LLP
One East Main Street, Suite 201
Madison, Wisconsin 53703

Shannon M. Bloodworth
PERKINS COIE LLP
607 Fourteenth Street, NW, Suite 800
Washington, D.C. 20005

s/William J. Heller
William J. Heller, Esq.

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